

A Pharmacotherapy Algorithm for Stabilization and Maintenance of Pediatric Bipolar Disorder

MANI N. PAVULURI, M.D., DAVID B. HENRY, PH.D., BHARGAVI DEVINENI, M.D.,
JULIE A. CARBRAY, D.N.Sc., MICHAEL W. NAYLOR, M.D., AND PHILIP G. JANICAK, M.D.

ABSTRACT

Objective: To assess the feasibility and effectiveness of an evidence-based pharmacotherapy algorithm in the treatment of pediatric bipolar disorder. **Method:** The study reports the results of a study of 64 bipolar type I subjects who were treated according to an algorithm developed in our specialty clinic. All subjects had been diagnosed using the Washington University in St. Louis Schedule for Affective Disorders and Schizophrenia. Subjects scored an average of 28 (± 4) on the baseline Young Mania Rating Scale. All subjects were assessed over an 18-month period. In addition, we were able to match 17 of the 64 subjects in the algorithm sample for gender, age, ethnicity, socioeconomic status, and diagnosis with an equal number of subjects in a psychopharmacology clinic who received treatment as usual. **Results:** Prescribing clinicians were able to implement primary and secondary strategies, including detailed tactics of medication choices in the algorithm group. Growth curve analysis of the total algorithm group showed strong and significant improvement in symptoms. Analyses of the matched groups also showed strong effects for the treatment algorithm over treatment as usual. Treatment adherence and family satisfaction were higher in the algorithm group. **Conclusion:** An evidence-based, problem-solving pharmacotherapy algorithm is feasible and may be associated with better outcomes in the treatment of pediatric bipolar disorder. Randomized trials will be necessary to gather additional support for the algorithm's effectiveness. *J. Am. Acad. Child Adolesc. Psychiatry*, 2004;43(7):859–867. **Key Words:** pediatric bipolar disorder, treatment algorithm, evidence-based medicine, psychopharmacology, clinical trial, mood stabilizer.

Although we continue to shed light on the nuances and course of pediatric bipolar disorder (PBD), more efforts are needed to develop empirically based treatments. Children are often treated with multiple medications in partial or excessive doses. In addition, there is often a

history of inadequate trial periods. Although randomized, controlled designs are ideal to determine the efficacy and safety of medications, investigators have not always been able to recruit or maintain subjects in such trials, in part because of the complex and refractory nature of PBD (Kowatch et al., 2000; Wagner et al., 2002). Furthermore, studies that had low attrition rates allowed rescue medications or continuation of stable drug regimens in addition to the study drug (e.g., methylphenidate for comorbid conditions such as attention-deficit/hyperactivity disorder [ADHD]) (Frazier et al., 2001; Wagner et al., 2002). Alternatively, studies that use a retrospective chart review method come closer to a real-life setting and underscore the myriad difficulties in pharmacological management of PBD (Biederman et al., 1996; Frazier et al., 1999). Such trials have been most helpful in informing us what not to do as much as what to do. For example, retrospective chart review data initially warned of the ill effects of antidepressants in PBD (Biederman et al.,

Accepted January 26, 2004.

From the Pediatric Mood Disorders Clinic and Bipolar Research Program, Department of Psychiatry, University of Illinois at Chicago (M.N.P., D.B.H., B.D., J.A.C., M.W.N.) and the Psychiatric Research Unit, Rush-Presbyterian-St. Luke's Medical Center (P.G.J.), Chicago.

This study was supported by funding from NIH MO1-RR-13987 (M.N.P.,PI), Campus Research Board Competition Award (M.N.P.,PI), and the Colbeth Foundation. In addition to the funds that supported this study, Dr. Pavuluri also receives research support from NIH 1 K23 RR018638-01, GlaxoSmith-Kline NeuroHealth, Abbott Pharmaceuticals, and Janssen Research Foundation.

Correspondence to Dr. Pavuluri, Institute for Juvenile Research, 840 South Wood Street (MIC 747), Chicago, IL 60612-7347; e-mail: mpavuluri@psych.uic.edu

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DOI: 10.1097/01.chi.0000128790.87945.2f

1996). Problems with these studies, however, included a lack of systematic diagnostic, symptom, or side effect measures; frequently poor reliability and validity of clinical charting; the absence of randomization or a systematic approach in the sequence of decision making; and multiple medications being simultaneously prescribed for various symptoms. Thus, we believe that a twofold approach is preferable. This includes (1) randomized, controlled trials (RCTs) to clarify the efficacy and safety of medication(s) and (2) prospective, protocol-based, problem-solving models that use existing evidence to inform us about the usefulness of a specific treatment algorithm. Our current study uses the second approach.

Existing treatment studies of PBD (Pavuluri et al., 2002) and algorithms for adult bipolar disorder (Janicak et al., 2001; Kahn et al., 2000) were carefully reviewed to construct the current problem-solving algorithm for PBD. This was then applied in a specialty clinic for pediatric mood disorders. Given the complexity of medication management in PBD, we wanted to test the feasibility of using such an algorithm in a tertiary care setting under the direct supervision of a research psychiatrist (M.N.P.) before applying it in a community setting. This study had two specific aims: (1) to identify and address practical difficulties that may arise in executing the treatment algorithm and (2) to assess the effectiveness of the algorithm in treating PBD as preliminary data for a larger RCT.

METHOD

DEVELOPMENT OF A PROBLEM-SOLVING ALGORITHM

Fundamental to effective treatment are accurate diagnosis and assessment of the severity of a manic episode. Tracking of treatment progress and feedback to the medication algorithm are also possible if the outcomes are carefully defined and monitored. The following definitions of symptomatic change were followed throughout the study: severe episode = Clinical Global Impressions Scale for Bipolar Disorder–Severity Scale (CGI-BP-S) mania scale score of ≥ 6 ; moderate episode = CGI-BP-S mania scale score of 4–5; mild episode = CGI-BP-S mania scale score of 2–4; no episode = CGI-BP-S mania scale score of ≤ 2 ; partial response = CGI-BP-S mania scale score of ≤ 4 ; no response = excessive side effects, CGI-BP-S mania scale score of >5 or lack of behavioral response.

The pharmacotherapy algorithm protocol was executed in two phases to reflect the naturalistic treatment process. The goal of the first phase was mood stabilization. The goal of the second phase was to address insufficient response, comorbidity, or other complications.

First Phase

Given the paucity of published data in PBD, the primary treatment strategies for mood stabilization were constructed based on scientific evidence from the existing literature, data from adult studies (Bowden et al., 2000; Sachs et al., 2002), and algorithms of adult studies (Janicak et al., 2001; Kahn et al., 2000) combined with expert opinion (Kowatch et al., 2003; Wagner, 2003). For the purpose of this paper, the levels of evidence are defined as A, B, and C (adapted from U.S. Preventive Services Task Force, 1996): level A = systematic review of RCTs with narrow confidence intervals; level B = systematic review of cohort studies with homogeneity, individual cohort study, or low-quality RCT (e.g., $<80\%$ follow-up) outcomes research; level C = systematic review of case-control studies, individual case-control studies, case series, and expert opinions with explicit critical appraisal.

- Evidence from level B studies (RCTs in children [Kowatch et al., 2000; Wagner et al., 2002]) combined with some consensus support based on the adult literature indicate that the primary agent is a mood stabilizer. Thus, divalproex sodium or lithium was used as the first choice in this study, followed by carbamazepine.
- Empirical studies also provide evidence that in more severe episodes (e.g., hospitalization), adding an antipsychotic was superior to monotherapy with either lithium (Kafantaris et al., 2001) or divalproex sodium (Delbello et al., 2002). There is also strong support for this approach from the adult literature on severe bipolar disorder (Bowden et al., 2000; Sachs et al., 2002). Therefore, combination therapy was included in the algorithm as the treatment of choice for more severe or psychotic mania.
- Second-generation antipsychotic (SGA) monotherapy was considered as a first-line option with predominant irritability and high CGI-BP-S aggression scores (i.e., >5). This was based on level C evidence such as anecdotal case reports and chart reviews (Frazier et al., 1999; Schreier, 1998) and open trials of olanzapine (Frazier et al., 2001) and risperidone (Faraone et al., 2003).

Second Phase

Adjuvant and/or secondary treatment strategies comprised this phase, and the tactics are based on level C evidence. In our model, more than one adjuvant strategy may have been used simultaneously to address coexisting or unresolved problems. They include the following.

Comorbid ADHD. Residual inattention and/or hyperactivity unresolved with the primary strategy of mood stabilization required a psychostimulant (e.g., long-acting forms of mixed amphetamine salts, methylphenidate, or dexamphetamine; the average daily dose of methylphenidate equivalent was 0.5 mg/kg). Level C evidence has demonstrated the use of stimulants for treating comorbid ADHD without accompanying worsening of symptoms of mania (Carlson and Kelly, 1998; Carlson et al., 2000).

Sleep Disturbance. If sleep difficulties persisted after adequate dosing of the primary medication taken at bedtime, to regain routine and ensure adequate rest for the child, adjuvant medications were trazodone 25 to 50 mg or clonidine 0.05 to 0.1 mg, in that order. Priapism occurs in 1 of 20,000 males with the use of trazodone (Feighner and Boyer, 1988). Therefore, parents were asked to report any prolonged erections for early intervention (Thompson et al., 1990).

Depressive Symptoms. With a discrete episode or resurgence of depressive symptoms in a mixed episode, patients were treated with lithium, lamotrigine, bupropion, or venlafaxine, in that order. Se-

lective serotonin reuptake inhibitors (SSRIs) were excluded as an option given the possibility of switching based on level C evidence (Wilens et al., 2003).

Autonomic Hyperarousal With Rage Attacks. If there was a partial resolution or breakthrough symptoms were unresolved despite adequate doses and length of trial, tactics included adding an SGA, an additional mood stabilizer with a different mechanism of action (e.g., combination of lithium and divalproex sodium) or clonidine, in that order.

Alternative SGAs. With predominant irritability and poor initial response with SGA monotherapy, quetiapine, ziprasidone, and olanzapine were considered, in that order, as monotherapy or a combination regimen if patients became severely ill or psychotic.

Alternative mood stabilizers included carbamazepine, oxcarbazepine, lamotrigine, and topiramate, in that order. Lamotrigine took precedence if there were significant depressive features.

IMPLEMENTING THE STRATEGIES AND TACTICS

Each subject was titrated to the optimal dose(s) of a mood stabilizer within the first week or the maximal dose tolerated with the exception of lamotrigine, which was increased more slowly at the rate of 12.5 mg per week. Subjects remained on the same dose(s) for an initial trial. An improvement of at least 1 point on the CGI-BP Improvement Scale (CGI-BP-I) score during the 3 weeks after achieving a full dose was required to continue on the first choice of mood stabilizer. If symptoms worsened, the initial agent was replaced with the alternative before the end of 3 weeks. Otherwise, a full trial of mood stabilizer or SGA was allowed for 6 weeks before switching. If the response was inadequate after 6 weeks on an SGA, subjects then received a mood stabilizer. If on mood stabilizer monotherapy, subjects were tried on a second mood stabilizer monotherapy before moving to the alternative tactic of augmentation with an SGA. The SGAs were introduced in the combination therapy arm if response was inadequate after 6 weeks before considering an alternative mood stabilizer. The maximal allowed dose and titration schedule were worked out for each individual drug. Titration was always in ascending order, but higher doses were omitted for children weighing <20 kg.

STUDY PROCEDURES

Subjects

This study was approved by the University of Illinois at Chicago Institutional Review Board. Parental consent and child assents were obtained. The pharmacotherapy algorithm was used to treat 64 subjects diagnosed with bipolar disorder type I, manic ($n = 38$) or mixed ($n = 26$) episodes. Subjects presented for treatment at our specialty clinic and satisfied the study's inclusion and exclusion criteria (algorithm group). We sought to identify control subjects (treatment as usual [TAU]) with bipolar disorder, also satisfying the inclusion and exclusion criteria, in a pharmacotherapy clinic ($n = 34$) in the same setting. These patients were referred either 2 months before or after the time of setting up our specialty clinic. A subsample of 17 subjects from the algorithm group (Young Mania Rating Scale [YMRS] 29 ± 3) was matched for gender, ethnicity, primary diagnosis, and socioeconomic status to 17 bipolar disorder type I subjects (YMRS 28 ± 6) who received TAU in the pharmacotherapy clinic during the same time period. The mean age of the entire study sample was 11.74 years ($SD = 3.36$ years). Mixed

episodes were present in 47.1% ($n = 8$) of the matched algorithm group and 35.3% ($n = 6$) of the TAU group.

Inclusion criteria for algorithm and TAU group were a diagnosis of *DSM-IV* bipolar disorder I manic or mixed episode determined by clinical interview and Washington University in St. Louis Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS), 5 to 18 years of age, and a score of ≥ 15 on the YMRS (Young et al., 1978). Exclusion criteria were active substance abuse during the previous 8 weeks, serious medical problems, the presence of another *DSM-IV* Axis I diagnosis that required psychopharmacologic treatment with the exception of ADHD, and laboratory values outside the normal range.

Baseline Measures

Initially, an unstructured, open-ended clinical interview was conducted with the parents and child separately. This assessment lasted 1 to 1.5 hours (M.N.P., J.A.C., child and adolescent psychiatry fellows). This was followed by a more extensive interview using the WASH-U-KSADS (Geller et al., 1998) within the first week of entrance into the study for both the algorithm and TAU samples. The WASH-U-KSADS interviews in both groups were completed by the same trained raters, a board-certified child and adolescent psychiatrist (M.N.P.), and doctoral-level nurse practitioner in child and adolescent psychiatry (J.A.C.). Based on the Cohen κ , the interviewers had an interrater reliability of 0.96 on individual items. The research diagnosis was established by consensus of the two interviewers. Family information was obtained using the Family History Screen (Weissman et al., 2000), revised with the authors' permission to include the grandparents' histories. Parents were queried about other risk factors and psychiatric history, including temperament, history of physical or sexual abuse, psychiatric hospitalization, and treatment.

Prospective Ratings. At each visit, progress was rated using the NIMH CGI-BP-I for overall change in symptoms of psychosis, mania, depression, aggression, ADHD, and sleep disturbance (Spearing et al., 1997). The CGI-BP-I was the primary efficacy measure because it tracks the multifaceted symptom picture of PBD. At the first and last visits, the principal investigator (PI) rated each patient in both the algorithm group and TAU group on the CGI-BP-S, the Clinical Global Assessment Scale (CGAS), and frequency of cycling. Ultrarapid cycling (5–365 cycles per year) and ultradian cycling (>365 cycles per year) were rated as present or absent based on the information obtained using the WASH-U-KSADS (Geller et al., 1998). A 75% reduction in the number of cycles in the month before posttreatment assessment from the number of cycles in the month before index study admission was considered substantial improvement. Adverse effects of medications were also recorded at each visit. A second board-certified child and adolescent psychiatrist (M.W.N.), independent of the research setting and blind to the clinician's CGI-BP-I ratings and group that the subjects belonged to (whether algorithm group or TAU), also completed the ratings on every second case. The interrater reliability was excellent for the overall improvement scale and the six subscales, ranging from 0.83 to 1.0, respectively, with a κ value of 0.96.

Clinician Training. Subjects in the algorithm group were treated by a board-certified child and adolescent psychiatrist (M.N.P.), a doctoral-level nurse practitioner in child and adolescent psychiatry (J.A.C.), and child and adolescent psychiatry fellows. Clinical supervision was provided by M.N.P. to other clinicians managing the algorithm group. Strategies, tactics, and prescribing rules are clearly defined. Mood stabilization is a primary strategy, and attempting to

treat breakthrough symptoms of psychosis and treating residual ADHD after primary mood stabilization are secondary strategies. Tactics are the specific medication choices such as lithium or divalproex sodium for initial mood stabilization. Rules on dosing are based on our pharmacotherapy manual developed for standardized use of medications. Since the completion of the study, we posted this manual on our Web site (www.psych.uic/pmdc). In addition, application of the algorithm was checked in a weekly meeting for every medication change by the research team to ensure adherence to the protocol. No additional training was provided for the board-certified child and adolescent psychiatrist treating the TAU group in the medication clinic, and this remained fiscally separate from the mood disorders clinic with no overlap in clinical involvement.

STATISTICAL ANALYSIS PLAN

On the CGI-BP-I, we had measures at multiple time points before and during treatment for each subject. However, all subjects did not have the same number of points of measurement. We used mixed-effects linear models to estimate the extent of improvement in subjects by examining their slopes across multiple measurement points on the CGI-BP-I. These models permit estimation of rates of growth using all available data. They differ from more traditional repeated-measures analyses in that even subjects with missing points of measurement can be included in a growth curve analysis. These analyses provide estimates of each subject's level and rate of change over time as well as tests of the extent to which groups of subjects differ on these estimates.

Some measures in this study were collected only at baseline and post-test. To analyze these measures, we used analysis of covariance, repeated-measures analysis of variance, or *t* tests for numeric measures and chi-square tests for categorical measures. These methods allowed us to compare medication groups on pre-/postchange or posttest levels.

RESULTS

PROGRESS OF ALGORITHM

The mean length of treatment was 30.2 weeks (7.02 months). Patient compliance measured in terms of the number of missed sessions was 0.63 (\pm 0.97). Patient satisfaction on an overall scale of 1 to 5 (1 = worst and 5 = best) that defines acceptability, availability, and efficacy was 4.6 (\pm 0.83).

First Phase or Primary Strategy of Mood Stabilization

Results of the first phase (or primary strategies for mood stabilization) are shown in Figure 1. Few subjects in the algorithm group were able to remain only on monotherapy over 6 months (n = 18; 28.1%). Only four subjects were able to remain on SGA monotherapy of the eight who received it (50%). A total of 40 subjects (36 who received mood stabilizer as first choice and 4 who failed SGA alone) received mood stabilizer monotherapy, and only 7 subjects (17.5%) showed

complete response. Of the 53 subjects (combination therapy as first choice in 20 + 33 who failed monotherapy) who received combination therapy, 33 (62.26%) attained complete response. Complete response was seen in 44 (68.75%) of the 64 subjects in the overall sample who received algorithm treatment. These results, along with those from the TAU group, are shown in Table 1. Average medication doses in the algorithm and comparison groups are shown in Table 2.

Second Phase or Adjuvant Strategies of Treatment

Psychostimulants were used in 19.0% of the algorithm group, as shown in Table 1. Doses of medications used as an adjuvant strategy to address residual symptoms or ADHD are summarized in Table 2.

IMPROVEMENT IN THE ALGORITHM GROUP

To determine whether improvement was significant in the algorithm group, we constructed a growth curve model of CGI-BP Overall Improvement Scale scores predicted by time in months, with gender, ethnicity, and age as covariates. This model showed a strong and significant negative parameter for time (B = -0.16, t_{269} = 8.34, p < .001). Thus, with each month, the group treated according to the algorithm improved on average by 0.16 points on the CGI-BP Overall Improvement Scale.

We conducted similar analyses of the CGI-BP Aggression, Mania, and Depression Improvement Scale scores. The slopes over time for the patients treated with the algorithm were significant and negative for aggression (B = -0.20, t_{331} = 10.35, p < .001), mania (B = -0.22, t_{331} = 10.47, p < .001), and depression (B = -0.14, t_{331} = 7.40, p < .001), indicating significant improvement on all these indicators. A final CGI-BP Overall Improvement Scale score of ≤ 2 was noted in 68.3% of the algorithm sample. The final mean CGAS score for the entire 64 patients treated with the algorithm approach was 56.19 (SD = 7.62).

PRE-POST DIFFERENCES IN MATCHED GROUPS

Next, we compared the matched groups of subjects treated according to the algorithm or TAU on pretreatment and posttreatment CGI-BP-S scores. We first conducted analyses to identify pretest differences between the algorithm and TAU groups. Both groups were comparable except for difference in age at onset

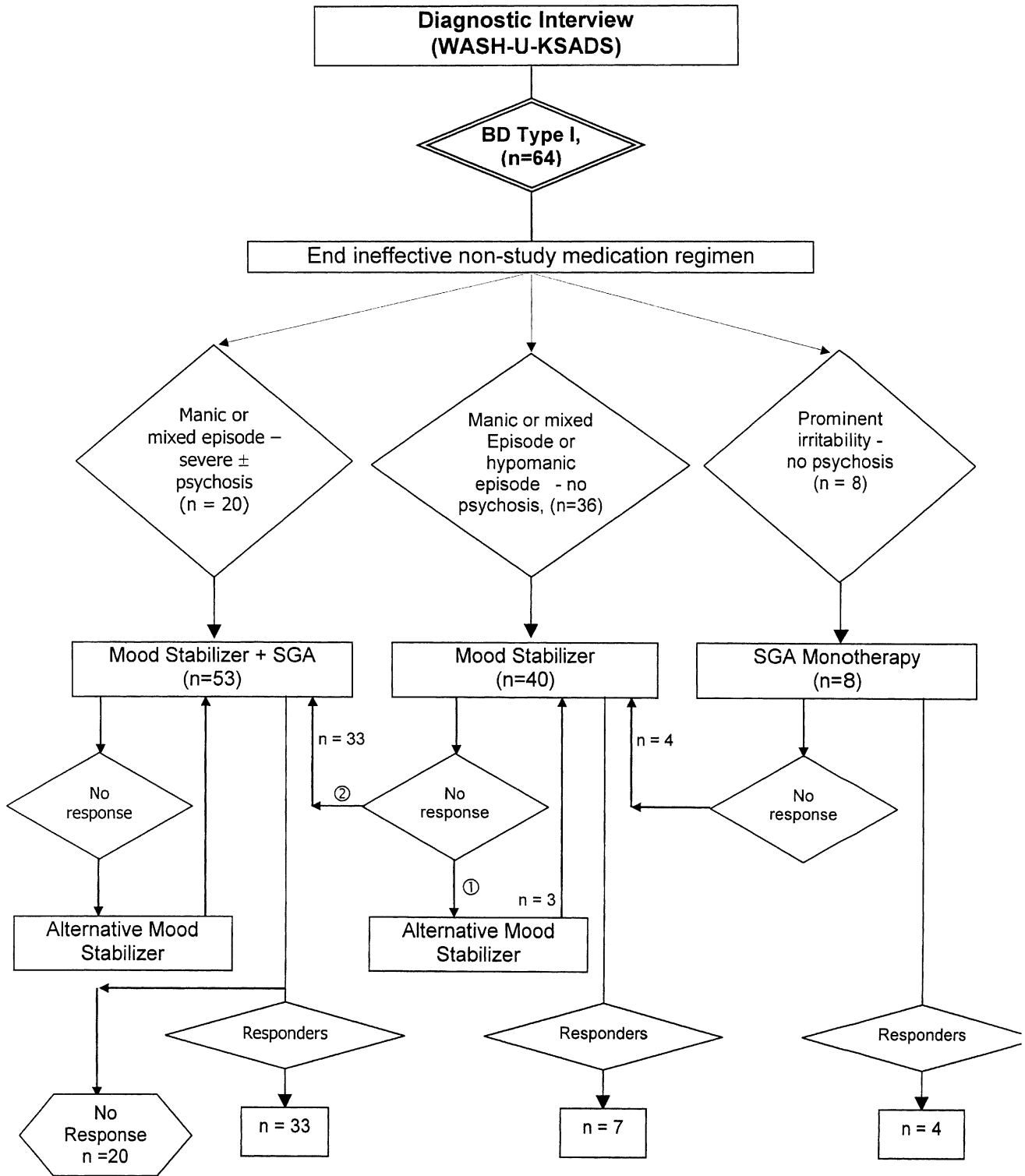


Fig. 1 Experimental pharmacotherapy algorithm: first phase. BD = bipolar disorder; SGA = second-generation antipsychotic; WASH-U-KSADS = Washington University in St. Louis Schedule for Affective Disorders and Schizophrenia.

TABLE 1
Comparison of Medication and Treatment Response: Total Algorithm Group and Matched Samples

Variable	Total Algorithm Group (<i>N</i> = 64)	Matched Samples	
		Algorithm (<i>n</i> = 17)	Treatment as Usual (<i>n</i> = 17)
Average no. of medications	2.14	1.94	2.06
Monotherapy at final visit (%)	28.1	23.5	23.5
Combination therapy at final visit (%)	71.4	76.5	0
Psychostimulants (%)	19.0	0	4.1
SGA ever (%)	77.8	82.4	17.6
MS ever (%)	61.9	70.6	64.7
Treatment response (%)			
CGI mania ≤ 2.0	39.7	47.1	0.0
CGI overall ≥ 2.0	68.3	94.1	0.0
Final CGAS, mean (SD)	56.19 (7.62)	55.41 (5.29)	38.82 (10.84)

Note: CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impressions Scale; MS = mood stabilizer; SGA = second-generation antipsychotic.

(i.e., all the TAU group had onset before 5 years of age compared with the algorithm group (39.1%) ($\chi^2[2, n = 34] = 15.92, p < .01$). Pretest comparisons of eight initial symptom severity scores on the CGI-BP-S subscales and initial core *DSM-IV* symptoms on the WASH-U-

KSADS returned only a single significant difference between the matched TAU and algorithm groups (i.e., TAU patients had higher CGI-BP-S ADHD scores at pretest than the algorithm group [means 5.88 versus 4.43, $t_{32} = 3.51, p < .01$]).

TABLE 2
Average Doses of Medications

Type of Medication	No. (%) and Average Dose (mg) for Matched Samples								
	Total Algorithm Group (<i>n</i> = 64)			Algorithm (<i>n</i> = 17)			Treatment as Usual (<i>n</i> = 17)		
	No.	(%)	Dose	No.	(%)	Dose	No.	(%)	Dose
Mood stabilizer									
Lithium	27	(43)	772	8	(47)	812	2	(12)	666
Divalproex sodium	7	(11)	727	3	(18)	600	8	(47)	794
Carbamazepine	4	(6)	572	1	(6)	710	1	(6)	557
Oxcarbazepine	3	(5)	700	0			0		
Second-generation antipsychotics									
Risperidone	46	(73)	0.99	13	(76)	0.98	2	(12)	1.58
Quetiapine	3	(5)	25.0	0			0		
Olanzapine	3	(5)	5.0	0			1	(6)	2.5
Ziprasidone	5	(8)	38.6	1	(6)	40	0		
Psychostimulants									
Adderall**	8	(13)	15.56	0			14	(82)	24.29
Methylphenidate*	4	(6)	14.38	0			2	(12)	29.75
Antidepressants									
Bupropion	1	(2)	139	0			0		
Other									
Clonidine	8	(13)	0.12	3	(18)	0.16	2	(12)	0.25
Trazodone	10	(16)	48.75	3	(18)	57	0		

* $p < .10$; ** $p < .01$.

We then conducted analyses for CGI-BP Overall Severity, Aggression, Mania, and Depression Scale scores using mixed linear models. This controlled for the matching, entering pretest age at onset and CGI-BP-S ADHD scores as covariates. There were significant and substantial differences by group (algorithm versus TAU) on three of the four measures. Algorithm patients had more positive outcomes on the CGI-BP Overall Severity subscale ($B = -1.99$; $F_{1,8.2} = 34.1$, $p < .001$), the CGI-BP Mania Severity subscale ($B = -2.67$; $F_{1,8.2} = 34.92$, $p < .001$), and the CGI-BP Aggression Severity subscale ($B = -3.02$; $F_{1,8.9} = 55.68$, $p < .001$). Results on the CGI-BP-S subscale and CGI-BP Mania subscale are illustrated in Figure 2. The effect on depression was not statistically significant ($B = -1.27$; $F_{1,11.73} = 4.16$, $p < .10$), but trended in the same direction. The treatment parameter estimates (the B statistics reported above) indicate the number of scale points separating the algorithm and TAU groups at post-test, controlling for pretest scores. The CGI-BP Overall score of ≤ 2 was seen in 94.1% in the matched algorithm group compared with none in TAU group. In addition, a t test comparison of posttest CGAS scores between matched algorithm and TAU groups showed a significant difference ($t_{32} = 5.67$, $p < .001$) with the algorithm group having higher CGAS scores at post-test (mean 55.41) than the TAU group (mean 38.82).

Treatment adherence (i.e., number of missed sessions) was also better in the algorithm group than the TAU group (algorithm group = 0.82 ± 0.95 ; TAU group = 2.88 ± 2.47). The t test difference between the matched groups was $t_{15} = 4.47$, $p < .05$. Scores on the Patient Satisfaction Scale were higher in algorithm group (4.8 ± 0.41) compared with the TAU group (3.1 ± 1.1). The t test difference between matched algorithm and TAU group on satisfaction was $t_{15} = 5.56$, $p < .05$.

Given that weight gain was one of the parameters in determining the choice of drug, this was tracked carefully. The average weight gain was 6 lb in the entire sample of algorithm group. It was 6.3 lb in the matched sample of algorithm and 5.7 lb in the TAU group with no significant differences in weight gain between groups. It was not possible to attribute weight gain to any specific medication given that many subjects are on more than one medication. None of the subjects developed metabolic syndrome with weight gain.

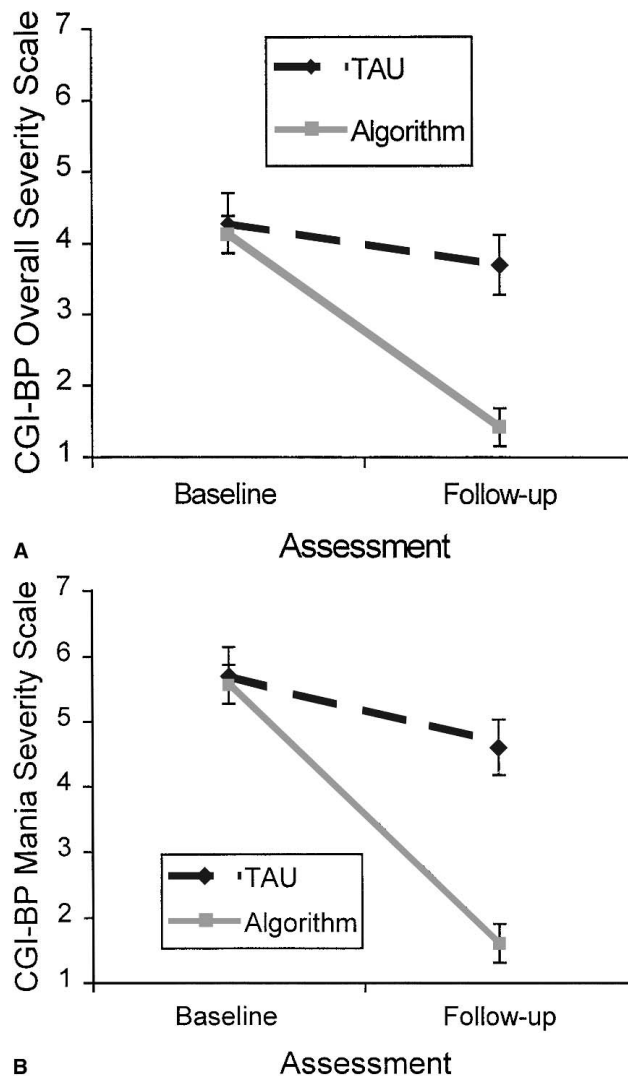


Fig. 2 Outcomes for the matched samples. A: The algorithm group had significantly lower overall severity at the final visit than the matched treatment as usual (TAU) subjects. B: The algorithm group showed lower mania symptom severity at the end of treatment compared with the TAU group.

DISCUSSION

To our knowledge, this was the first attempt to implement and evaluate an evidence-based algorithm for the treatment of PBD. Overall, the algorithm protocol proved to be feasible. A specific titration rule was used that allowed flexibility of dosing during the first and second phases of treatment. Mood stabilizers or SGAs were prescribed earlier in the algorithm group compared with the TAU group, in which the majority received stimulants before mood stabilization. Although the number of medications used in the algo-

algorithm group did not differ from the TAU group, the choice of medications and response rates did differ, favoring the algorithm group. Thus, inappropriate medications (e.g., antidepressants or stimulants as primary strategy), high doses, and an excessive number of medications were avoided in the algorithm group.

A number of unexpected situations emerged in implementation of the algorithm. For example, some patients worsened after initially improving. If patients were on a combination regimen of mood stabilizer and SGA, we had to decide which medication to change first. We opted for altering the SGAs first, with changes in mood stabilizer as the second tactic. Weight gain was a major issue with all primary medications, particularly the SGAs. It varied on a case-by-case basis as to whether the weight gain was significant enough to the patient to discontinue the current medication choice despite a full clinical response. There was flexibility in drug choice to avoid medications that were previously ineffective or caused significant side effects. At times, this precluded a retreat of potentially effective medications. Similar to the problem encountered in ADHD algorithm study by Pliszka et al. (2003), fixed-dose titration in ascending order was not always possible. For example, tolerability or severity of illness dictated a less or more aggressive titration for some. Side effects usually led to reducing the dose as a first rule (especially if a good response was noted) instead of discontinuing the medication altogether. In two cases, irritability (associated with aggression) and depression were present and moderately severe. With some patients who were candidates to receive either a mood stabilizer or an SGA, our choice was made easier by parents who did not want their children on a mood stabilizer because of side effects. This illustrates the current state of practice in which a clinician's judgment may be affected by the opinions of well-informed parents. It is hoped that these scenarios will be used as a springboard for further psychoeducation and execution of appropriate clinical decision in collaboration with parents.

Clinical Implications

Given the complexity of bipolar disorder in children with predominantly mixed picture of manic and depressive symptoms, chronicity, irritability, rapid cycling, and comorbid ADHD, a clear decision-making framework is necessary because clinicians need to ad-

dress more than one problem simultaneously. Our results are consistent with those of others (Kowatch et al., 2000; Wagner et al., 2002) in which monotherapy does not appear to be efficacious and combination therapy yields a better response (Delbello et al., 2002; Kafantaris et al., 2001; Kowatch et al., 2003). This model will allow combination therapy in cases of partial response to initial mood stabilization and avoid haphazard prescription of multiple medications. It allows a close collaboration between families and clinicians, especially when treatment resistance is encountered where strategies can be explained in an understandable manner.

Limitations

Although our TAU group was a matched sample, it was a convenience sample and we recognize the importance of a randomized trial in the future. A second methodological issue is that it was conducted in a tertiary setting and at a single clinical site. Although our clinic operates as a community clinic, its organization, support, and resources may not be similar to those of a medication clinic run by trainees in a tertiary setting or a community mental health center. However, introducing this model of treatment, at its minimum, is intended to influence the clinicians in implementing an organized framework of medication management for PBD. Inherent bias of a single-site study is tackled in part by getting an independent rater to rate the detailed clinical material blind to the clinician's rating to establish interrater reliability. Additionally, all the ratings were obtained prospectively. However, we cannot eliminate the bias intrinsic to an open trial in documenting the clinical outcome by the authors. Another controversial issue with regard to the design of the algorithm is whether the second drug in combination therapy should be a mood stabilizer or SGA, a contentious issue that also applies to choosing the first drug of choice. We based our strategies on adult studies (Bowden et al., 2000) as well as those in youth (Delbello et al., 2002; Kafantaris et al., 2001) in using combination therapy of mood stabilizer and SGA versus two mood stabilizers such as lithium plus divalproex sodium as first-line combination strategy. Given the rapid progress in clinical trials using SGA, it is likely that several of these SGAs will be considered as mood stabilizers in the future, similar to olanzapine,

risperidone and quetiapine at the current time. This may influence our future clinical practice.

Despite these limitations, we believe that this trial is an important step toward demonstrating the feasibility of our algorithm, which improved treatment adherence and was satisfactory to most families. We believe this preliminary study illustrates the effectiveness of our algorithm in PBD complicated by issues such as partial response to primary strategies, comorbidity, breakthrough symptoms, depressive episodes, and sleep difficulties.

Disclosure: Dr. Pavuluri serves as a consultant to Bristol-Myers Squibb Company, Janssen Pharmaceuticals, Abbott Laboratories, and Glaxo, Smith, and Kline Neurohealth.

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